Criteria for Non-formulary Use of Buprenorphine Sublingual Tablets

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel
Prepared by: F. Goodman, PharmD, BCPS; A. Gordon, MD, MPH; D. Kivlahan, PhD;
G. Dalack, MD; J. Pope, MD; L. McNicholas, MD, PhD; R. Suchinsky, MD

These criteria are based on the best clinical evidence currently available. The recommendations in this document are dynamic, and will be revised as new clinical information becomes available. This guidance is intended to assist practitioners in providing consistent, high quality, cost effective drug therapy. These criteria are not intended to interfere with clinical judgment; the clinician must ultimately decide the course of therapy based on individual patient situations.

INTRODUCTION

Buprenorphine is a Schedule III partial opioid agonist that was approved by the FDA for the treatment of opioid dependence on October 8th, 2002. It is the first agent available in the U.S. for office-based treatment of opioid dependence under the Drug Abuse Treatment Act of 2000 (DATA 2000), which allows specially qualified physicians to prescribe Schedule III to V drugs for treatment of opioid dependence in an office setting. The main objective of this law was to expand access to treatment for opioid dependence by incorporating the management of opioid dependence into mainstream primary care. The implementation of buprenorphine in the VA will require careful consideration and planning.

VA CRITERIA FOR USE

Provider criteria

The provider must

- be a *qualifying physician* as defined by DATA 2000 with the exception that, in the VA, individual physicians but not group practices are limited to treating 30 patients;
- meet all SAMHSA and DEA notification and registration requirements for the Opioid Treatment Waiver Program (available at: http://www.dpt.samhsa.gov),

AND either

- have experience in addiction medicine or addiction psychiatry;

OR

- if inexperienced in addiction medicine, treat patients who have already been converted from methadone to buprenorphine at a VA-supported opioid agonist treatment [OAT] center (based on Patient Criterion #2) and who remain stable or who do not need close supervision.

In the VA, physicians treating patients with buprenorphine for opioid dependence must write a valid waiver identification number on each prescription for buprenorphine.

Facilities must set up a process to verify that providers are authorized to prescribe buprenorphine for treatment of opioid dependence.

Local non-formulary criteria should require that a patient referral for necessary ancillary services be made and the referral appointment date be provided before authorizing a prescription for buprenorphine.

Non-physicians are prohibited from prescribing buprenorphine.

It is the physician's responsibility to make sure the necessary resources (such as referrals for ancillary treatment, cross-coverage by a qualified physician, urine drug screening, and secure medication storage) are in place before prescribing buprenorphine.

Similarly, *before* converting a stable patient from methadone to buprenorphine in accordance with Patient Criterion #2, the physician should make sure a qualified physician is available to accept the patient upon the patient's transition from an OAT center to primary care.

Patient criteria

Buprenorphine is indicated for opioid substitution (maintenance) treatment of opioid dependence in

1) New patients not currently receiving OAT
   AND who meet at least one of the following 3 criteria:
   - Do not have timely access to a VA-supported OAT center.
   - Do not meet regulatory criteria for treatment in a methadone or LAAM program.
   - Will have difficulty adhering to scheduled visits at a VA-supported OAT center because of restrictive clinic hours.
2) Appropriately selected patients on stable methadone maintenance who have difficulty adhering to scheduled visits at a VA-supported OAT center or may not need close supervision. Opioid treatment programs should determine the criteria for appropriate selection of these patients, and the criteria should take into consideration such factors as the likelihood that the patient would remain stable on low doses of methadone (≤ 30 to 40 mg daily), and the patient's psychosocial adjustment, lifestyle stability, and job stability.
3) Patients who do not obtain desired outcomes with methadone.
4) Patients who have a documented severe, uncontrollable adverse effect or true hypersensitivity to methadone or its homologue, LAAM.

In general, methadone should remain the substitution treatment of choice.

New patients who can be referred to a VA-supported OAT center in a timely fashion should receive methadone or LAAM.

When patients cannot make the required daily clinic visits for methadone treatment or when timely access to methadone treatment is not possible, treatment with LAAM (dosed 3 times a week) should be considered before buprenorphine.

Criteria for use of buprenorphine for medically supervised detoxification are not yet available as its role in detoxification is evolving.

The use of buprenorphine and buprenorphine/naloxone for discontinuation of methadone or LAAM maintenance therapy may be considered on a case-by-case basis in patients who do not tolerate a tapered dosage reduction of either drug or the use of alpha$_2$-adrenergic agonists (e.g., clonidine) for blocking withdrawal symptoms.

See *Inappropriate Indications for Use* below.

DATA 2000 definition of qualifying physician

Physicians who satisfy conditions 1 through 3 below.

1. Meet one or more of the following training requirements:
   - Hold a subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties.
   - Hold an addiction certification from the American Society of Addiction Medicine.
   - Hold a subspecialty board certification in Addiction Medicine from the American Osteopathic Association.
   - Have completed not less than 8 hours of authorized training on the treatment or management of opioid-dependent patients. This training may include classroom situations, seminars at professional society meetings, electronic communications, or other media. The American Society of Addiction Medicine, American Academy of Addiction Psychiatry, American Medical Association, American Osteopathic Association, and the American Psychiatric Association are all authorized to provide this training.
   - Have participated as an investigator in one or more clinical trials leading to the approval of a narcotic drug in schedule III, IV, or V for maintenance or detoxification treatment, as demonstrated by a statement submitted to the Secretary of Health and Human Services by the sponsor of such approved drug.
   - Have such other training or experience as the State medical licensing board (of the State in which the physician will provide maintenance or detoxification treatment) considers to demonstrate the ability of the physician to treat and manage opioid-dependent patients.
   - Have such other training or experience as the Secretary considers to demonstrate the ability of the physician to treat and manage opioid-dependent patients. Any criteria of the Secretary under this subclause shall be established by regulation. Any such criteria are effective only for 3 years after the date on which the criteria are promulgated, but may be extended for such additional discrete 3-year periods as the Secretary considers appropriate for purposes of this subclause. Such an extension of criteria may only be effectuated through a statement published in the Federal Register by the Secretary during the 30-day period preceding the end of the 3-year period involved.
2. Have the capacity to provide or to refer patients for necessary ancillary services, such as psychosocial therapy.
3. Agree to treat no more than 30 patients at any one time in their individual or group practice (see exceptions for VA and OAT programs in footnote below).

Exception to item #3 of DATA 2000: The Center for Substance Abuse Treatment (CSAT) has designated that, in the VA, the limit of 30 patients applies only to individual physicians. There is no limit on the number of patients that can be treated with buprenorphine for group practices. The 30-patient limit also does not apply to OAT programs.

Further information on DATA 2000 and physician qualifying requirements can be obtained at http://buprenorphine.samhsa.gov. The VA's Centers of Excellence in Substance Abuse Treatment and Education (CESATEs) are also available for advice and consultation on buprenorphine. Contact Laura McNicholas at 215-823-6085 or mcnicholas_l@mail.trc.upenn.edu (Philadelphia) or Daniel Kivlahan at 206-768-5483 or Daniel.kivlahan@med.va.gov (Seattle).

INAPPROPRIATE INDICATION FOR USE

Pain management. The off-label use of sublingual buprenorphine solely for pain management cannot be supported at the doses available in the U.S. The doses used for opioid maintenance therapy (minimum 2 mg) are five to ten times higher than those evaluated for acute pain (0.2 to 0.4 mg per dose).[1-5] The dose of sublingual buprenorphine for opioid dependence is generally higher than those used for chronic pain; however, the lower total daily doses of sublingual buprenorphine used for opioid dependence overlap with the upper end of the dosing range evaluated for chronic pain (e.g., 2 to 16 mg per day vs. 0.4 to 3.2 mg per day).[6-9] Opioid maintenance doses of buprenorphine are generally given in a single daily dose while analgesic doses have usually been given in divided daily doses (analgesic duration: 6 to 9 hours). In the U.S., buprenorphine sublingual tablets in strengths lower than 2 mg are not available and the tablets are not scored. There is a significant risk of overdose if a patient not currently tolerant to opioids were to receive a 2-mg dose. The optimal dose, the adequacy of analgesia with once daily dosing, and the superiority of buprenorphine over full opioid agonists have not been

established. Patients who require therapy for acute or chronic pain and who are not being treated for addiction should be managed using standard analgesic treatments.

Buprenorphine-maintained patients with pain may experience pain relief due to buprenorphine, but the drug should generally not be used primarily for analgesia. These patients should be treated with a trial of non-opioid analgesics while continuing buprenorphone maintenance. If stronger opioid analgesics are required for either acute or chronic pain, then buprenorphine should be discontinued. It should be noted that buprenorphine may block or displace other opioid agonists from receptor sites and can precipitate withdrawal. When buprenorphine is to be restarted, recommended induction doses should be initiated at least 12 hours after the final dose of the opioid analgesic to avoid precipitating withdrawal.

There are no studies that have examined the analgesic effects of buprenorphine during maintenance therapy. The once daily administration of sublingual buprenorphine as recommended for opioid maintenance therapy may provide insufficient pain relief. The optimal dose of sublingual buprenorphine in the simultaneous management of both opioid dependence and pain is not known.

DOSAGE AND ADMINISTRATION

Buprenorphine is available as a single drug in 2- and 8-mg tablets and as a combination of buprenorphine and naloxone in 2 mg/0.5 mg and 8 mg/2 mg tablets. Naloxone was added to discourage the intravenous misuse of buprenorphine. When taken orally or sublingually, naloxone has poor bioavailability, although blood concentrations of the drug are detectable. If given sublingually to opioid-dependent individuals after the opioid agonist effects have abated, naloxone is unlikely to produce clinically relevant effects. However, if sublingual naloxone is given to these individuals before the agonist effects of the opioid have diminished, precipitated withdrawal may occur. Buprenorphine/naloxone, when misused intravenously, is highly likely to precipitate intense withdrawal symptoms in individuals dependent on other opioid agonists.

Buprenorphine alone is recommended for induction and the buprenorphine/naloxone combination is recommended for maintenance or when clinical use includes unsupervised administration. Unsupervised administration of buprenorphine alone should be limited to patients who cannot tolerate naloxone (e.g., patients with a documented hypersensitivity to naloxone).

Buprenorphine is generally administered once daily. More frequent administration of divided daily doses may also be used, and less than daily dosing (e.g., three times weekly) is possible for maintenance therapy. The tablets must be taken sublingually, allowing 5 to 10 minutes for the tablets to completely dissolve. Oral administration of the tablets reduces the bioavailability of the drug.

A brief summary of dosing recommendations are provided here. For more detailed instructions on dosage and administration of buprenorphine, consult appropriate references such as the *Buprenorphine Curriculum for Physicians* and *Buprenorphine Clinical Practice Guidelines* available from the Center for Substance Abuse Treatment (CSAT) (see http://buprenorphine.samhsa.gov/bwns/Curriculum.html).

The use of buprenorphine should be part of a comprehensive treatment plan that includes detoxification and psychosocial treatment modalities. As with other controlled drugs used in the treatment of opioid dependence, providers should take appropriate precautions to prevent the diversion and abuse of buprenorphine.

Induction

For induction, the use of buprenorphine alone is recommended over the buprenorphine/naloxone combination product, although there have been no studies comparing the two products for induction and there is no contraindication to using the combination product for induction. It is important to start induction with buprenorphine when signs of early opioid withdrawal have appeared, taking into consideration the type of opioid dependence.

Day 1

Patients physically dependent on heroin or other short-acting opioids

Initiate buprenorphine at least 4 hours, preferably at least 12 to 24 hours, after the patient last used opioids or preferably when the patient exhibits definite signs of withdrawal. The maximal recommended induction dose of buprenorphine is 8 mg on day 1 (given at once or in divided doses as clinically indicated).

Patients physically dependent on methadone or other long-acting opioids

The criteria for nonformulary use of sublingual buprenorphine require that a patient have a documented severe, uncontrollable adverse effect or true hypersensitivity to methadone or LAAM before the physician considers

switching to buprenorphine. Patients who are stable on methadone or LAAM maintenance and who do not have a compelling reason to switch therapy should continue maintenance on methadone or LAAM.

Limited controlled experience with the conversion of methadone-maintained patients to buprenorphine suggests that precipitated withdrawal symptoms are possible, particularly in patients maintained on methadone doses greater than 30 to 40 mg daily or when buprenorphine is started shortly after the last methadone dose. Therefore, to avoid precipitating withdrawal symptoms when conversion from methadone or other long-acting opioid to buprenorphine, it is recommended that the dose of the long-acting opioid be tapered to the equivalent of methadone 30 to 40 mg daily or less and the last dose of methadone be taken at least 24 hours before starting buprenorphine. The induction dose of buprenorphine should start at a minimum of 2 mg, repeating doses as needed up to 8 mg in 24 hours.

There are no studies evaluating induction with buprenorphine in LAAM-treated patients. The CSAT document *Buprenorphine Clinical Practice Guidelines* (available at: http://buprenorphine.samhsa.gov) recommends that the dose of LAAM be tapered down to 40 mg or less every other day and buprenorphine should be started at least 48 hours after the last dose of LAAM. The induction dose of buprenorphine should start at a minimum of 2 mg, repeating doses as needed up to 8 mg in 24 hours.

Day 2 and onward

If no serious adverse effects or evidence of withdrawal emerge within two hours of the administration of a dose, the patient is ready to move on to the next step in induction. On day 2, the dose should be advanced by 2 to 4 mg. The buprenorphine/naloxone combination should be started on day 3 at the same dose as day 2 (e.g., 12 mg/3 mg if 12 mg buprenorphine was given on day 2) then titrated to achieve an adequate maintenance dose.

Using the buprenorphine/naloxone combination product, adjust the buprenorphine dose in increments or decrements of 2 or 4 mg per day to a level that holds the patient in treatment and suppresses opioid withdrawal effects. The recommended target dose of buprenorphine is 12 to 16 mg per day to be achieved within the first week, unless adverse effects occur. Should adverse effects occur, the dose of buprenorphine should be maintained or decreased until these adverse effects abate. If patients continue to have problems adjusting to buprenorphine (experiencing withdrawal symptoms or feeling compelled to use illicit drugs), the dosage may need to be increased more rapidly.

Physicians should attempt to achieve an adequate maintenance dose, titrated to clinical effectiveness, as quickly as possible to prevent the patient from developing undue opioid withdrawal symptoms. In some studies, gradual induction over several days led to a high rate of dropouts during the induction period. In one study, buprenorphine 8 mg was given on day 1 and 16 mg on day 2. Induction was accomplished over 3 to 4 days depending on the target dose.[10]

Stabilization (approximately one to two months)

The induction phase is completed and the stabilization phase has begun when the patient has discontinued or markedly reduced the use of illicit drugs, is experiencing no withdrawal symptoms, is experiencing minimal or no side effects, and no longer has cravings for the drug of abuse. Dosage adjustments may still be necessary during this period. Doses may be increased in 2- to 4-mg increments per week until stabilization is achieved. The majority of patients should stabilize on doses between 12 to 16 mg, but doses can be increased up to 32 mg.

Maintenance

For induction and stabilization, once daily dosing of buprenorphine is preferable. For maintenance, once daily dosing has also usually been used; however, less frequent dosing of buprenorpine is possible due to the drug's long duration of action.

Alternate-day dosing,[11-15] thrice weekly,[16-18] every-third-day,[15,18] and every-fourth-day[18] dosing of buprenorphine have been studied. In general, the same total equivalent weekly dose is given in divided doses over extended dosing intervals.

Most of the published trials evaluating extended dosing intervals have used buprenorphine alone.[11-18] A single trial has investigated the buprenorphine/naloxone combination.[12] Physicians are advised to consult a specialist in opioid dependence treatment before deciding to use extended dosing intervals with buprenorphine/naloxone.

Dosage reduction and treatment discontinuation

The decision to discontinue treatment with buprenorphine or buprenorphine/naloxone should be made as part of a comprehensive treatment plan in partnership with the patient. There have been no controlled trials comparing different methods of tapering doses; therefore, the best method of discontinuing treatment has not been determined. Both gradual and

abrupt discontinuation of drug have been used, but gradual dosage reduction in stable patients is preferred. Withdrawal symptoms upon abrupt discontinuation or rapid taper of buprenorphine tend to be delayed and milder than with full opioid agonists.

Dosing in special populations

Hepatic disease: Plasma concentrations of buprenorphine and naloxone, which are both extensively metabolized, are expected to be higher in patients with moderate and severe hepatic impairment. Dosage should be adjusted and the patient monitored for symptoms of precipitated withdrawal.

Renal disease: No specific recommendations for dosage adjustment are given. There have been no differences in buprenorphine pharmacokinetics in dialysis and normal individuals. The pharmacokinetics of naloxone in renal failure are unknown.

Patients admitted to hospital: Under DATA 2000, physicians without a waiver are allowed to *continue* buprenorphine treatment in patients who are already receiving buprenorphine and are admitted to a hospital (such physicians are not allowed to *start* buprenorphine treatment). When a patient on buprenorphine is admitted to a hospital, consultation with a qualified physician or addiction specialist should be obtained.

Quantity Prescribed

Prescriptions for buprenorphine should have no refills and should be limited to a 7-day supply during the induction period and a 30-day supply at any time. Exceeding the 30-day supply limit may be considered only under extraordinary circumstances.

MONITORING

Patients must be closely supervised and monitored at the clinic for several hours after administration of each induction dose. Therefore, appropriate space and trained nursing support are needed to manage patients during the induction phase. Supervised administration of the initial maintenance doses is also recommended.

As patients improve, unsupervised administration and take-home supplies of buprenorphine may be considered. Consult appropriate references for more detailed recommendations on monitoring frequency.

Hepatic events ranging from cytolytic hepatitis to hepatic failure have been observed in addicts during treatment with buprenorphine. A causal relationship to buprenorphine is unclear. Pre-existing liver enzyme abnormalities, viral hepatitis, hepatotoxic drugs, and illicit intravenous drug use may be causal or contributing factors in the development of hepatic events. Liver enzyme tests should be checked at baseline and periodically thereafter.

The potential of buprenorphine to prolong the QT interval has been demonstrated in vitro[19] but there have been no published clinical reports of buprenorphine-related cardiac arrhythmias or QT prolongation. Electrocardiographic monitoring is not recommended at this time.

DRUG INTERACTIONS

CYP 3A4 inhibitors or inducers: If CYP 3A4 inhibitors or inducers are co-administered with buprenorphine, patients should be closely monitored and dosage adjusted if necessary. Increased plasma concentrations of buprenorphine have been observed when it was co-administered with the potent CYP 3A4 inhibitor, ketoconazole. Dose reduction may be indicated if buprenorphine is given with CYP 3A4 inhibitors such as azole antifunal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), HIV protease inhibitors (e.g., ritonavir, indinavir, and saquinavir), the antidepressant, nefazodone, or grapefruit juice. The interaction between buprenorphine and CYP 3A4 inducers (e.g., phenobarbital, carbamazepine, phenytoin, and rifampicin) has not been studied.

CNS depressants: Patients who receive buprenorphine with other central nervous system (CNS) depressants (e.g., other opioid analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative-hypnotics, or alcohol) may experience increased CNS depression. Consider reducing the dose of one or both agents if the two agents are co-administered. Buprenorphine tablets, taken orally or sublingually or by injection, has been implicated in fatal drug abuse-related overdoses, particularly when used with benzodiazepines.[20-22]

COST

The VA acquisition cost for buprenorphine/naloxone is $2.93 for the 8-mg tablet and more than one half of that for the 2-mg tablet (Table 1). VA prices for buprenorphine without naloxone were not available.

Table 1 Drug acquisition costs for opioid agonist treatments

	Buprenorphine/Naloxone			Methadone				LAAM	
	2 mg/d tab	8 mg/d tab	16 mg/d tab	20 mg/d disp tab	80 mg/d disp tab	20 mg/d conc	80 mg/d conc	20 mg 3x/wk soln	80 mg 3x/wk. soln
Cost/Dose	$1.66	$2.93	$5.86	$0.08	$0.33	$0.06	$0.26	$0.29	$1.18
Cost/Mo	$49.65	$87.84	$175.68	$2.46	$9.84	$1.96	$7.84	$3.48	$14.16

Prices reflect lowest VA-State Veterans Base prices for buprenorphine and lowest Federal Supply Schedule prices for methadone and LAAM as of 27 May 2003. Prices for buprenorphine without naloxone were not available.

Further information on buprenorphine can be found in the *National PBM Drug Monograph: Buprenorphine and Buprenorphine/Naloxone* available at: www.vapbm.org or vaww.pbm.med.va.gov.

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